REMARKS/ARGUMENTS

Claims 4-6, 10, 15, 19, 32, 39-40, 45, 49, 52-54 and 57-64 are pending in the application. Only claims 54 and 56 are under examination, i.e., the remaining claims have been withdrawn by the Examiner from further consideration in this application as being directed to a non-elected invention. Claim 54 has been amended, *inter alia*, as suggested by the Examiner's comments at pp. 3-4 and 9-10 of the Office Action. The claim amendments are all supported by the application as filed and thus the entry of these amendments is respectfully requested. Upon such entry claims 4-6, 10, 15, 19, 32, 39-40, 45, 49, 52-54 and 57-64 will remain pending with claims 54, as amended, and 57 under examination.

Claim Rejections Under 35 U.S.C. §112, First Paragraph – Scope of Enablement

Claims 54 and 57 are rejected under 35 U.S.C. §112, first paragraph. The Office Action alleges that the specification is enabling for a method for treating acute or chronic renal failure in a human or animal patient exhibiting a) at least one dysfunction of endothelial progenitor cells, b) hypertension and c) at least one end-organ damage, wherein the at least one end-organ damage is selected from the group consisting of left ventricular hypertrophy, microalbuminuria, proteinuria and glomerular filtration filtration rate of 30 to 80 ml/min, said method comprising administering to said patient a pharmaceutical composition comprising a subpolycythemic dosage of from 1 to 90 IU/kg of body weight per week of erythropoietin or Aranesp, wherein the acute or chronic renal failure is thereby treated in said human or animal patient.

On the other hand, the Examiner alleges that the specification does not provide enablement for a method for treating acute or chronic renal failure in a human or animal patient exhibiting a) at least one dysfunction of endothelial progenitor cells and b) at least one cardiovascular risk, wherein the at least one cardiovascular risk is selected from the group consisting of hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance and hyperhomocysteinemia and c) at least one end-organ damage wherein the at least one end-organ damage is selected from the group consisting of cognitive dysfunction and increased thickness of the intima media in the carotid artery, said method comprising administering to said patient a pharmaceutical composition comprising a subpolycythemic dosage of from 1 to 90 IU/kg of body weight per week of at least one of

erythropoietin and a derivative thereof, wherein the acute or chronic renal failure is thereby treated in said human or animal patient.

Claim 54 has thus been amended as shown above, i.e., substantially as suggested by the Examiner, and these amendments are believed to overcome the majority of the Examiner's grounds for rejection under 35 U.S.C. 112, first paragraph. However, even as amended, the claim retains the language "at least one of erythropoietin and a derivative above" which the Examiner has objected to. In regard to the inclusion of the subject terminology in claim 54, the Examiner indicates on p. 8 of the Office Action that the specification would not support claims to EPO polypeptides modified to an unlimited extent relative to those exemplified. The Examiner then goes on to state that a skilled artisan would have to carry out experimentation on an astronomically large number of possible structural variants in order to find those that would operate effectively in the claimed method. Applicants, however, respectfully traverse even this aspect of the Examiner's rejection.

Applicants' method is directed to the proposition that a particular group of patients, i.e., as recited in claim 54 for example, can be treated in a particular manner, namely using a subpolycythemic dosage of EPO which, therefore, does not raise the haematocrit value and which leads to prevention, diminution or slowing of damage to kidney tissue and/or to regeneration of damaged kidney tissue. The effects attributable to the subject method rely on the use of erythropoietin which according to specification pages 21-25, constitutes a protein with the biological activity of erythropoietin. Thus, the specific protein is not decisive in achieving the aims of applicants' process – so long as a protein is used that has the biological activity of erythropoietin (see, e.g., specification p. 21, first and last paragraph).

The biological activity of erythropoietin is well known among those having at least an ordinary level of skill in the relevant art and is described at pp. 21-25 of the specification. This thus enables a skilled artisan to readily determine whether a specific protein falls within the scope of, "at least one of erythropoietin or a derivative thereof". Further, the description set forth at pp. 21-25 provides specific examples of some EPO derivatives useful in the present invention, including Aranesp, CERA, EPO-α and EPO-β. Further, p. 22 provides structural information regarding how the "derivatives" as used in this context are defined.

For the reasons express above, applicants respectfully submit that they believe that the teachings provided in the present specification adequately enable not only the use of

erythropoietin, but also derivatives thereof. It is, furthermore, advanced that to limit applicants' invention to a very specific erythropoietin form would tend to deprive them of any reasonable reward for the discovery of their invention since the teaching to use the presently described method could easily be applied to a derivative of erythropoietin readily found in the prior art and which would be, if the Examiner's objection is upheld, outside the scope of the main claim. An inventor should obtain for its discovery a reasonable scope of protection in accordance with the teachings provided concerning said invention and applicants respectfully submit that the teaching provided in the present specification sufficiently enables one of at least ordinary skill in this art, with a reasonable effort – i.e, without the need for any undue amount of experimentation, capable of finding those variants of erythropoietin that would work in the claimed method, namely those having the biological activity of erythropoietin.

The Examiner is thus respectfully requested to reconsider and withdraw the enablement rejection under 35 U.S.C. 112, first paragraph, maintained from the previous Office Action as described at pp. 3-4 of the present Office Action.

Further to the above, on p. 9 the Examiner makes a new claim rejection of claims 54 and 57 under 35 U.S.C. 112, first paragraph. The claims are rejected based on an alleged failure to comply with the written description requirement. The Examiner, moreover, characterizes the rejection as a "new matter rejection". The rejection is respectfully traversed.

In particular, the Examiner alleges that the specification does not support the recitation of "increased insulin resistance" as set forth in claim 54, but that it only supports "insulin resistance". In response to this ground for rejection, applicants note that claim 54 has been amended above to recite only hypertension as the at least one cardiovascular risk factor. This amendment, then, renders moot the ground for rejection under 35 U.S.C. 112, first paragraph – lack of written description (new matter), which should therefore be withdrawn.

Claim Rejection Under 35 U.S.C. §103

Claims 54 and 57 are rejected at pp. 10-11 under 35 U.S.C. §103 as being allegedly unpatentable over Jungers et al. in view of Stehouwer et al. for the reasons set forth at pp. 11-13 of the Action. The rejection is respectfully traversed.

Claim 54 is the only rejected claim written in independent form. In its present, i.e., amended, form the claim is directed to a method for treating acute or chronic renal failure in a

human or animal patient exhibiting a) at least one dysfunction of endothelial progenitor cells, b) hypertension, and c) at least one end-organ damage, wherein the at least one end-organ damage is selected from the group consisting of left ventricular hypertrophy, microalbuminuria, proteinuria and a glomerular filtration rate of 30 to 80 ml/min., wherein the method comprises administering to the patient a pharmaceutical composition comprising a subpolycythemic dosage of at least one of erythropoietin and a derivative thereof, wherein the acute or chronic renal failure is thereby treated in the human or animal patient by at least one of prevention, diminution or slowing of the damage to kidney tissue and regeneration of damaged kidney tissue.

Turning first to Jungers et al., i.e., the primary reference in the cited combination with Stehouwer et al. relied upon by the Examiner to reject the pending claims, applicants submit that Jungers et al. analyze the influence of recombinant human EPO therapy on the rate of progression of chronic renal failure in pre-dialysis patients. The results reported in the reference are based on the background conditions that are thoroughly explained in the introduction and in the discussion portion of the subject reference. As indicated therein, once the first EPO treatments have been successfully applied to anemia patients who were already dependent upon dialysis, i.e., patents that do not produce any endogenous EPO due to a total lack of renal function, the treatment was also extended to those renal failure patients (those suffering from chronic renal failure or "CRF") who were not yet undergoing dialysis.

The reference evidences a concern, however, that administering EPO to such pre-dialysis patients in order to correct anemia would lead to negative consequences, such as an increase in the blood pressure of the patient (see, e.g., p. 307, right-hand column or p. 311, right-hand column, last paragraph). The Examiner's attention is also respectfully directed in this regard to the corresponding comprehension discussion found on p. 301, line 3 to the right-hand column, first paragraph. The portions of the reference cited to above thus clearly establish that there were major concerns expressed in the prior art regarding the correction of anemia by administration of EPO in pre-dialysis patients. Conflicting data, however, also existed in the prior art that deleterious effects were not to be expected from such therapy.

The authors of the Jungers et al. reference thus retrospectively evaluated the situation. They compared the rate of decline of renal function in pre-dialysis patients which, accordingly, have a less advanced stage of CRF. These patients were either treated with erythropoietin in a moderate dose of 54.3 IU/kg/week. Another group was not treated with EPO and thus these

patients represented a control group (see, e.g., the Abstract and p. 308 "Results" column, second paragraph). All of the patients were anemic patients – meaning patients having reduced hemoglobin levels.

Jungers et al found that treating the pre-dialysis CRF patients with moderate dosages of erythropoietin achieves an effective and sustained correction of the anemia without inducing a worsening of blood pressure or adverse effects on renal function (see p. 311, right-hand column, last paragraph). In fact, a substantial delay until renal replacement therapy requiring dialysis was needed was observed. In sum, therefore, Jungers et al. teach that administration of moderate doses of EPO in pre-dialysis patients delays the need for those patients to undergo dialysis. Therefore, such administration serves to extend the pre-dialysis phase. In contrast to the disclosure contained in the prior art, the extension of the pre-dialysis phase resulting from administration of moderate dosages of EPO in pre-dialysis patients produces no adverse effects upon such patients. Such treatment leads to the partial correction of anemia, meaning that the patients have higher levels of hemoglobin (Hb) – compare Table 2, Hb at end for EPO+ and EPO- groups to Table 1, Hb values for EPO+ and EPO- group. Jungers et al. also disclose, on p. 309 in Table 3, that within the EPO+ treated group, half of the patients (i.e, 10 patients) demonstrated a so-called slow progression, while the remaining ten patients demonstrated an unchanged progression of CRF.

At p. 311 of the Jungers et al. reference, the right-hand column, second full paragraph discusses the beneficial effects of EPO and associates these effects with an alteration of tissue hypoxia, meaning an insufficient oxygen supply which, in the context of Jungers et al. is clearly referencing an anemia-caused insufficiency in the oxygen supply. This teaching, thus, may be taken to mean that the hypoxia is due to the reduced Hb level which, according to the EPO treatment described in Jungers et al., is raised during the course of the EPO treatment. Thus, the effects discussed in the Jungers et al. reference are clearly due to the hemoglobin-increasing effect of the moderate EPO doses.

In contrast, therefore, to the disclosure contained in the Jungers et al. reference, the presently claimed method is not intended for increasing the subject's hemoglobin value. In fact, applicants' claims specifically recite the usage of a subpolycythemic dosage of EPO which, according to the teachings provided in the present application, refers to a dosage which does not influence the Hb value. Claim 54 refers to a subpolycythemic dosage of at least one of EPO and

a derivative thereof. As indicated above, such a dosage does not lead to any significant increase in the hemoglobin (Hb) value and, therefore, it can not be considered to constitute a moderate dose such as the dosage taught for use in Jungers et al., which significantly increases the Hb value.

Applicants note, moreover, in regard to this issue that claim 54, prior to amendment herein, referred explicitly to an EPO dosage of 1 to 90 IU/kg body weight per week. However, this numerical range only spans the principally applicable dosage range, which is further limited by the specific requirement that the dosage to be applied is a subpolycythemic dosage. A "subpolycythemic" dosage, however, is not limited to the indicated range. The decisive feature is that the dosage be subpolycythemic, as is taught at pp. 44-45 in the present specification. Applicants have, therefore, further amended claim 54 to remove the preferred dosage range therefrom, while retaining the language that the dosage must be subpolycythemic, i.e, one that does not lead to an increase in the haematocrit of a subject. Thus the claim amendment is believed to serve to further clarify an important feature of the presently claimed method in that the subpolycythemic dosage recited in claim 54 does not cause an increase in the subject's haematocrit, whereas the dosage taught for use in Jungers et al. serves, in contrast, to significantly increase the Hb value.

Since Jungers et al very clearly link the beneficial effect of prolonging the pre-dialysis phase to the correction of an anemic condition, namely by raising the Hb level, it would be totally unexpected by one having an ordinary level of skill in the relevant art that a dosage which does not raise or alter the Hb value, i.e., a subpolycythemic dose, would have any effect on the conditions specified in applicants' claims.

In point of fact, the presently claimed method is not directed to the treatment of anemia, but instead teaches one of ordinary skill in this art that the claimed subpolycythemic dosage of at least one of EPO and a derivative thereof (see, e.g., claim 54), which does not cause the Hb level to rise, has structural effects on the damaged kidney tissue and prevents or reduces damage to the kidney tissue itself. The indicated effect, therefore, has nothing to do with the treatment of anemia because it is exerted on the level of the renal tissue, namely at the cellular level. The effect is, therefore, totally unexpected based on the teachings contained in Jungers et al.

In summary, Jungers et al. does not teach or even suggest that a subpolycythemic dosage of EPO or derivative has any effect as regards the therapeutic function recited in, e.g., claim 54.

Furthermore, the subject reference also does not provide any indication that EPO treatment has a direct, non-anemia-based effect on the regeneration of damaged kidney tissue - as is shown in the examples provided in the application. Thus, Jungers et al. neither teaches nor even suggests the method recited in applicants' claims presently under examination.

Applicants recognize, of course, that the present rejection is based not just on Jungers et al. alone, although that is the 'primary' reference, but rather, on the combination of Jungers et al. with the Stehouwer et al. reference. The Stehouwer reference is included in the combination, as indicated on p. 12 of the Office Action, due to its teaching that microalbuminuria, hypertension, endothelial dysfunction and an increased risk of left ventricular hypertrophy are aspects in CRF patients. The Stehouwer et al. reference, however, does not remedy the deficiencies, noted above, of the Jungers et al. reference. That is, it does not disclose or suggest the effectiveness of the subpolycythemic dose of EPO/derivative in achieving the resulting effect specifically recited in, e.g., claim 54. In fact, the reference does not provide any disclosure as to the dosage of EPO to be administered, nor any specific disease(s) to be treated or any specific group of patients to be treated. Thus, even when taken together with Jungers et al., the cited combination still does not teach or even suggest the presently claimed method to one having an ordinary level of skill in this art.

For all of the reasons above, therefore, the Examiner is respectfully requested to reconsider and withdraw all of the rejections of applicants' claims and to issue a Notice of Allowance directed thereto.

THIS CORRESPONDENCE IS BEING SUBMITTED ELECTRONICALLY THROUGH THE PATENT AND TRADEMARK OFFICE EFS FILING SYSTEM ON August 4, 2010

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